thing to me is the normalization of the kidney and the hepatic function which you showed.

I don't think any BiVAD can give you comparable data. I may be wrong on that, but we have never had that kind of experience at Barnes Hospital, so I think that is something that should be kept in mind.

The other question I have is in the study, you have strictly avoided applying this technique to the patients who previously had an LVAD or a BiVAD, and I would like to know what your plan is when you put your market material, what you are going to advise, because it seems to me it would be wrong to restrict it to that group in the first place. I would like to hear about that.

DR. COPELAND: We have no data from our study to support the use of this device in failed LVADs or BiVADs, but I would see personally, just on a personal basis, I would see no reason for not using it in the appropriate situation.

I would like to call on Dr. Banayosy, if I could, because I know they have experience in transitioning bridge to bridge, and I think they have even done a third bridge with this type of transition from an LVAD to a total artificial heart

with great success with a failing LVAD or a failing BiVAD.

Aly, could you speak about that?

DR. TRACY: I would ask you to restrict your comments, though, to things that are in that panel packet, if you can. Otherwise, it really doesn't enter into the purview of this panel.

DR. El-BANAYOSY: We have in our patient population, we have more than 45 patients, right now we complete analysis of 41 patients. About 40 percent of those patients had previously other mechanical circulatory support systems and failed, and we went to total artificial hearts.

DR. FERGUSON: Could I ask him a question? I think it is pertinent to find out because the device, whatever you put in the packet information is going to be used in that way, I think.

The question is, in those individuals who have devices in place, and then you put in this device, does that significantly increase the difficulty, the degree of surgical difficulty?

DR. El-BANAYOSY: It is not easy to replace an assist device with total artificial heart, but it is manageable and with experienced surgeons, you will be able to do that, and there

were significant causes why we switched from VADs to artificial heart.

In one case, I remember that we had a big thrombus, and the patient, after putting in a BiVAD system, and the patient was atrial cannulation, and because of severe heart failure, clot in his left ventricle, we had big thrombus formation, and we had no other chance with this patient other than to change the device.

With another patient, we had low flow states and the patient was in severe multiple organ failure, and to survive the patient, we had to give him more flow, and we had to replace the system to survive the patient.

In each case, there was a significant cause why to do that and to take the risk of the surgery.

DR. FERGUSON: Thank you.

I have one last question, and this relates to the fact that I am very, very impressed with the safety of the device in terms of the man years of use that you have put it to, but my question goes to the ruptured diaphragm, and I would like to know what you did to assure yourself that this was an anomaly, and not something that might come up down

the line.

MR. SMITH: We attempted to analyze the failure every way possible and worked with the FDA to see if there was anything else that we could do. At the end of that whole process, there was nothing that we could put our hands on like a manufacturing or a lot number or anything like that to point to that.

So, we will continue to monitor for that as a potential and we have set up a system that will be part of the training in order to diagnose that.

If you remember, that specific failure was not catastrophic, so if we can recognize it, we can provide an option to go in and replace that ventricle if it does happen, but again we looked, not only at our own experience in the study, but we went back in the design of the system and looked in the European, et cetera, and again all I can tell you is that it is a rare situation, but it doesn't necessarily mean that it won't happen again.

DR. TRACY: Dr. Krucoff.

DR. KRUCOFF: I also want to acknowledge the obvious, that the level of interest in their patient care and dedication to dealing with this

incredibly sick patient population across the investigators is very evident, and I will join everybody in saying thank you for trying to put the data on the table, but I have to say that I am very troubled that we are spending a lot more time talking about the practice of medicine and judgment than data that would actually support indications or help us understand.

Having just finished a clinical trial, a multi-center trial in 600 patients having acute large myocardial infarctions with a device that literally every single investigator with a passion was convinced was a better way to take care of them, at the end of the day, what the data show is actually we were harming them.

That is where I think ultimately, we have to try and realize that data that has so many deficiencies that you are left with many more questions than answers is a hard basis to bring a device forward with assurance that it is safe and effective, and these are very vulnerable patients. That means they have a whole lot more to gain from an effective new breakthrough therapy.

It also means that they potentially have a whole lot more to lose if the clustering slide,

such as, Dr. Copeland, you showed us earlier, if that clustering is not driven by the patient, but is actually driven by the device, and obviously, when those events start to cluster, people die. I don't know from the data we have which one is the chicken and which one is the egg.

I would appreciate it, though, because I think the interest in figuring out whether we can help this very ill patient population is clear.

Dr. Copeland, if you would help walk me through some of what I am still trying to get a feel for is what is perceived as better and what is perceived as worse.

Is it fair to say that, as a bridging device for these very ill patients, that the basic concept here is that use of the total artificial heart would be better than no other device, is that fair?

DR. COPELAND: Better than no device?

DR. KRUCOFF: Better than not using a device.

DR. COPELAND: Absolutely, no question.

DR. KRUCOFF: Then, compared to, let's start with LVADs, because if I heard Dr. Long correctly, and I may have misheard him, what I

heard him say was that it would be a difficult to do a randomized trial in this patient population because LVADs are so superior, did I mishear that?

DR. LONG: The technology is superior in terms of its sophistication and giving patients quality of life, but not the outcome particularly in a patient population that needs biventricular support. In fact, it is much worse.

DR. KRUCOFF: So, randomizing them would not be an option?

DR. LONG: LVAD against biventricular support?

DR. KRUCOFF: Against the total heart.

DR. LONG: I think it would be undesirable because I don't know you would--you are really dealing with two separate patient populations. You are dealing with a patient population that needs an LVAD alone, and a patient population that needs biventricular support, and I see those as two different patient populations that you would approach with different therapies.

DR. KRUCOFF: What I am trying to get ahold of is where are the indications. In fact, Dr. Long, I think you said that this total artificial heart is clearly intended for a very

specific patient population, but the patients who are included in this study, this one-arm study, and the patients who are the very specific patient population, I am having a hard time sorting out how you would put in indications, or separate them, or think about a way of actually proving where this is the same or where this is better.

So, the assumption is that in patients with biventricular failure, the assumption that I am hearing is that the total artificial heart would be better than just a left ventricular assist, is that fair?

DR. COPELAND: Absolutely.

DR. KRUCOFF: The other thing I heard I think from Dr. Pae was that it might even be that with the use of a total artificial heart, that it might be better to allow the total artificial heart to provide some of the other systemic normalization and actually do transplantation later compared to immediate transplantation. Is that also fair, Dr. Pae?

DR. PAE: If you were to look at the patient population that is very, very ill with impending multi-organ failure, and you transplant those individuals, they don't do well.

We also know that individuals that are put on devices and are allowed to normalize their function, and then are transplanted, are better, and that is one of the reasons that I had personally proposed the idea, and it is now part of the UNOS regulations, that we decide when to make those individuals--

DR. KRUCOFF: So, I heard you right, is that fair?

DR. PAE: Yes.

DR. KRUCOFF: Then, what I have heard through the presentations today is that the total artificial heart would certainly be better in these sick patients than putting no device at all, that in patients who have biventricular failure, the total artificial heart would certainly be better than just an LVAD, and that actually it might be better to use a total artificial heart and provide some physiologic support before transplantation rather than rushing to transplantation while these were all sick.

I guess I wanted to walk back through that, because better, to me implies superior, and ultimately, in every comparison with all the waffling about the inadequacies of comparisons,

what I am still at a loss for is where is the data that shows that there is a patient population that we can actually define where these folks do better.

Even when you responded to Dr. Yancy, and we cut them by pulmonary artery pressures, RV failure at least by one, even though earlier I think you acknowledged that one hemodynamic measurement doesn't define these folks, they are more complicated than that, and I appreciate that, but ultimately, we need some kind of way of understanding whether the intuition and the obvious inclination to practice medicine by using this device where you think it is going to be better, that there is actual data that we are not wrong.

DR. COPELAND: If I may respond to that. Let me say that this is not an intuitive thing that just comes into your mind and you are a clinician and you know that a guy needs a total artificial heart, so you are going to put one in. If that is what we presented today, then, I guess somehow I just totally missed the boat.

What we presented is very sick patients who were extremely ill. In fact, if you take the UNOS group of patients who are the sickest group of patients waiting for transplant, half of those

weren't sick enough even to enter into this study, and you take a group that is similar to them, not exactly like them, I mean even if you randomized, you probably wouldn't get all the characteristics exactly alike, but if you take a group that is similar and you show that they die in a very short period of time, and that the other ones live, then, I guess, you know, you have made a case for using the device.

That is the first part. The second part is how do you identify these patients and why do you put in a total artificial heart, and the answer is very simple - so the patients will live, and that is a multifactorial answer. It includes things like inotropic use.

We take patients that are this sick, and we put in an LVAD, do they come off inotropes? No. Does their liver failure get better? No. Does their renal failure get better? Sometimes yes, sometimes no, often they need dialysis. Some programs put in a dialysis catheter at the same time they put in their LVAD. Is the mortality rate any better? No.

We may not be able to, in words and numbers, exactly define what the entry criteria

are, but we have taken a group of patients who are extremely sick and who are not candidates for a VAD, and we have shown that they can survive, get transplanted, and be the same as the UNOS patients who have never had any kind of device.

That is a proof of sorts, and it is a clinical proof, and this is a clinical meeting here, and we are appealing to the clinicians on this panel to try to understand what it is that we have done, but it is a clinical proof that we can identify patients with biventricular failure who are dying, and we can do the right thing for them, and we have lots of evidence that if you do the other thing, the results aren't as good.

So, from looking at it as a continuum, the beginning and the end of the study, I think my conclusion would be that, in fact, we have described a group of patients who were dying and who benefited from a total artificial heart, and we have described them as best we can. I hope the panel doesn't get stuck on the criteria that we thought of in 1991, when we designed the study, that are being used as inclusion and exclusion criteria, as the ways in which patients are going to enter into this therapy, because it's not.

These are patients who are all on multiple inotropes, who have fulfilled Criteria A and B, who are sick and dying, who have right heart failure, who are maybe on a cardiopulmonary bypass, a ventilator, in renal failure and liver failure, and so forth, and that is the group that we are looking at. These are the very, very sick patients.

DR. KRUCOFF: So, can you help me then understand just out of the denominator patients you have presented from this 10-year experience, what percentage of them were not candidates for a VAD?

DR. COPELAND: Okay. What are you--

DR. KRUCOFF: Of the actual patients in your study--

DR. COPELAND: Yes?

DR. KRUCOFF: --what percentage of them were not candidates for a VAD?

DR. COPELAND: None of them were candidates for VADs. They got a total artificial heart. Are you talking about the control group or the implant group?

DR. KRUCOFF: No, the implant group.

DR. COPELAND: VAD was ruled out. We were instructed by the FDA you have to find reasons that these people are not candidates for VADs before you

put in a total artificial heart.

We looked at every single patient and tried to justify putting in an LVAD. Why? We, like everyone else want to send our patients home, so the hospital bill is not as high.

But in the end, that is not the priority, is it? The priority in this business is to prevent death, it is not to send the patient home from the hospital for the duration of his bridge to transplant. It is to save his life, so that he can get a transplant, and I would say that that is what happened.

DR. KRUCOFF: So, is the list of RV thrombus, arrhythmias, are those the criteria that were used to characterize these folks were not a candidate for a VAD?

I guess what I am trying to do, Dr. Copeland, is understand, since while you started this in '91 and '92, we are sitting here in 2004, and to understand how an indications for use could be styled, so that the intention, which is very clear from your investigators, is actually carried forward as the device goes to patients.

DR. COPELAND: Could you pull up LVAD3, please.

[Slide.]

This is sort of an exhaustive list of reasons for using a total artificial heart rather than an LVAD. Many of these indications were present, perhaps all of them in at least one of the patients in our study, but you can see that there are a number.

There are also, as Dr. Dembitsky said a few moments ago, situations where nothing but a total artificial heart will do, an LVAD won't do, a BiVAD won't do. A LVAD won't do because of right heart failure, a BiVAD won't do because of flow restriction. A BiVAD will only pump about 5 or 6 liters a minute. The total artificial heart pumps 7, 8, 9 liters a minute, and there are reasons for that.

So, patients do better who are very sick, who have that much blood flow, and what this device does is it gives them that flow.

DR. KRUCOFF: So, this is the kind of list that would characterize the way you identify patients who are not VAD candidates, who would be preferable total artificial heart plus maybe some other hemodynamic flow-related parameters like you just described.

DR. COPELAND: Yes, these are basically clinical scenarios.

DR. KRUCOFF: Have any of these clinical scenarios been compared to your event clustering and prediction of failure with this therapy?

DR. COPELAND: I think when you talk about event clustering, you need to think back to that slide we showed just before the event clustering, that is, that they not only cluster, but most of them occur in the first two days after implantation, so that these are very sick patients, and they are coming in to have a big operation, and they get sick.

They get adverse events, and all of the different sicknesses and complications they get are classified in one way or another as an adverse event.

Can we go back to S1, please.

[Slide.]

I just want to show this again to reemphasize that, yes, the events are clustered. They are clustered with respect to patient. In other words, if one patient has more than 12 events or 13 events, he is probably going to die, the mortality rate is very high, but most of those

events are also clustered with respect to time, and they are going to occur in the first two days or certainly in the first three weeks, so it reflects not only upon--well, it reflects I think mainly upon how sick the patient is before he comes in.

DR. KRUCOFF: It might reflect on a patient population that is more vulnerable to having this manipulation than other options.

DR. COPELAND: I don't think they have any other option. The other option in these patients, as we showed in the very first slide of this presentation, is death, and if you can get them to transplant, they don't do as well with transplant because they are crashing.

They are circling the drain, they have dysfunction of their kidneys and liver, and you put a transplanted heart into them, those are the ones that drive the mortality rate for heart transplantation up.

So, they are a sick population, that is a problem. We are just trying to present a solution to that problem in these very, very sick patients.

DR. KRUCOFF: Just another two questions. In terms of the planned duration of use, it sounds like we have at least one example of a couple of

years, and you mentioned it is important to discuss with patients the possible ramifications, if a heart is not ready, or whatever, their lifestyle.

Have you successfully reclaimed these devices? Obviously, when the patient gets their heart transplant, these devices come out. Have you all looked at the actual devices, the explants?

DR. COPELAND: Yes, we have.

DR. KRUCOFF: Any sort of concern over time? Is there a concern over time, do they show changes over time?

DR. COPELAND: No, we have not documented any change over time in terms of wear, surfaces, and we have documented any signs of thrombus, no matter how small, and what we have found is very minimal.

DR. KRUCOFF: Just as a footnote, and my last question is on training, but just as a footnote, for patients who really are at death's door, who really do not have any other option, there is a whole other path, the human device exemption path, that looks at data very differently than this type of purported safety and efficacy clinical trial, where ultimately, the assertion that there is superiority to any other available

technology would be a question that would relate to an analysis of data.

My last question is on training. Dr. Long mentioned that these things, once they go in, there is still a lot of important intensive interaction in their post-procedural management.

In the training program, is there a component to the training program for the ICU staff or for post-procedural management envisioned? I either didn't see that, I just wonder whether that is in the plans for training how to put this thing in, obviously, that has got to be done, beyond that, is there a plan for training the unit staff how to handle these folks?

DR. COPELAND: Actually, in total artificial hearts, as opposed to LVADs, the postoperative care is not really much of a challenge. The patients don't need inotropes. They usually have good end organ function. They get up and around. But there are certain other things, as you mentioned, that are important.

Certainly, nurses being familiar with the device and knowing how it works, knowing how to care for the drivelines is very important.

A second element is an anticoagulation

team, and we have established an anticoagulation team with algorithms and protocols for the administration of our anticoagulants and antiplatelet agents, and daily follow-up. I think that is a very important part of preventing thromboembolism.

Thirdly, there has to be an equivalency to the engineering team. It doesn't necessarily have to be an engineer, but it has to be somebody that is friendly with the hardware, knows how to plug in and unplug the air pressure lines, knows how to turn on and off the air tanks, so the patients can be moved around the hospital with the least amount of problems, because these patients do get up and walk around and sit on the patio, go to the wellness center, go down to the cafeteria and have lunch because they like the food down there better, and so forth.

I mean they lead sort of a, quote "normal" life within the hospital, but in order to do that, there has to be a special team that allows them to have that kind of mobility.

DR. KRUCOFF: It sounds like you and Dr. Long certainly share the vision, and I guess my suggestion would be that some sort of sense of how

you train that team would be worth thinking about.

DR. COPELAND: Absolutely.

DR. KRUCOFF: How about the patient, I didn't see at least the kind of discussion you alluded to, patient expectations around the device. Are there patient education materials that are either available or planned that would help the patient understand what those various ramifications are likely to be?

DR. COPELAND: Yes, there are, and that is one of the advantages of the transplant center. Most transplant centers have a team of nurse coordinators that center around the transplant program.

In our program, we have simply asked those nurse coordinators to take on additional responsibility in terms of the training of the patients, not only in their device and their medications on the device, but preparing them then for the transplantation and eventual immunosuppression that they are going to have.

DR. KRUCOFF: Thank you.

DR. TRACY: Dr. Maisel.

DR. MAISEL: Thank you.

I won't belabor many of the concerns that

I have had and have been addressed eloquently by some of the people up here today.

One of my concerns is the extrapolation of this device and this data to real life. Certainly, I think that concern becomes greater when we start comparing it to perhaps literature about LVAD, which I know we are not maybe making a direct comparison, but many of those published studies are in real life patients, and not just study patients.

I am interested in getting at a little bit of what you feel the learning curve is. Dr. Copeland, maybe you would best be able to speak to this.

After how many cases do you feel that you reached your adequate experience or your best experience where the complication rate may decline to a steady level? I would also be interested in see some data to that regard, in other words, complication rates for surgeon's first five or 10 implants versus the later implants.

DR. COPELAND: My guess is that modern surgeons in a transplant setting, who are used to transplanting the human heart will not have much trouble with the total artificial heart since the operations are very much the same.

In my opinion, it is easier to implant a total artificial heart than it is to put in a BiVAD or an LVAD. A BiVAD and an LVAD operation involve tunneling and pockets and manipulations that are somewhat difficult and require a fair amount of sophistication. A regular transplant surgeon can put in a total artificial heart quite easily.

We often help our residents put in these devices, so I can assure you that it can be done fairly easily. I think the things in the learning curve that are going to be important for surgeons who are taking this on for the first time, are going to be more thought problem oriented than mechanical.

They are going to be faced with situations where judgments need to be made. For instance, when the chest is closed and the cardiac output goes down, what do you do. Well, you open the chest and you reposition the device.

When the patient is in the ICU five hours after the operation and the output goes down and the CVP goes up, what do you do? Well, you take him back because his atria are tamponaded.

Those kinds of things can be taught, but those are judgmental things that an experienced

artificial heart person will act on perhaps more quickly than someone who is just starting.

So, there are some issues I think for starting up, and if I may, I would like to invite Banayosy one more time to speak since they just started up a program in the end of 2001 and have put in about 45 of these things, and see if he thinks there are--you know, because it is fresher in his mind than it is mine.

DR. MAISEL: I am interested in your opinion about how many--I mean we can listen to him, as well, but I am interested in your opinion about how any devices you think need to be implanted before the complication rate reached a steady state lower level.

I think we are all in agreement that it is likely there would be a higher complication rate in the first few implants for a physician. Maybe you disagree with that.

DR. COPELAND: You want a number?

DR. MAISEL: Yes.

DR. COPELAND: I would say probably a minimum of two, a maximum of five, something like that, somewhere in that range to get a good feeling for the range of common complications and how to

deal with them.

DR. MAISEL: I guess the next question I have is related to the training program where I am concerned that physicians get trained and they do some animal implants, but they don't actually witness an implant in a person, and I am wondering whether that is an issue.

DR. COPELAND: We have a videotape, of course, of implants. We certainly could write that in as one of the requirements before starting a program, or we could make a rule that provided an experienced surgeon be present at the time of the first one or two implants, something like that.

DR. MAISEL: I think at least speaking for myself, I think at least one witnessed implant in a human would be a reasonable expectation for a physician who is going to be implanting that device.

My other issue relates to the proposed post-approval follow-up, and you have suggested following up the enrolled patients for up to one year.

I am concerned that given the high rate of device problems that arise, that there will be a flurry of malfunctions or seemingly device-related

malfunctions, and it will be very difficult to sort out whether those are just the normal device-related malfunctions or whether there is something actually going on.

So, I would propose actually that there be a post-approval device registry for all implants. It doesn't sound like there will be an enormous number of implants each year, maybe in the hundreds at least initially, maybe slightly higher than that, but something that would require tracking of all device-related malfunctions and survival to transplant.

I think those numbers would be key for appreciating how this is working in the real world, and you would need both numerator and denominator to make those assessments.

Would you be opposed to something like that?

DR. COPELAND: Not at all. I think that is an excellent idea.

DR. MAISEL: Finally, I just had one other question touching on something that Dr. Tracy mentioned. We have talked about a body surface area minimum cutoff, and I was wondering if you could show any data related to success of the

device related to body surface area.

DR. COPELAND: I don't have any on hand, no. It is of interest, I think, that the two fit patients, fit problems that we reported, both of those patients were large, so fit problems can occur even in larger patients, and the surgeon has to be aware of positioning of the device, but I think that would be an interesting question, but from the very start, we have had that fairly rigid criterion of 1.7 square meters and greater, and the other criteria that I mentioned, so we really have not had a whole lot of experience putting this in smaller patients or trying to.

DR. MAISEL: Just as a follow-up, how was that number arrived at? You seemed to indicate that that number seems less important to you, but it is the only contraindication in the labeling. Why was that number picked?

DR. COPELAND: Well, it dates back to the history of this device that now is some probably 10 to 15 years old, this device and its predecessor, and sizing studies that were done and published that were based upon outcome results and size.

I just don't have memory of that literature now, but that is how it was inherited by

us, and it has been used generally pretty successfully, but as I said, it is not an absolute.

In other words, a small person with a large cardiac size can certainly have this type of device implanted, but I think great care has to be used by those deciding to do the implant that this is going to work. That is another part of the learning curve.

DR. MAISEL: Thank you.

DR. TRACY: Dr. Blumenstein.

DR. BLUMENSTEIN: I have two issues. The first is I am concerned about the validity of displaying data comparing to the reference cohort on a Kaplan-Meier plot, because as I was mentioning earlier, I am not sure that the baseline date determined for patients in the intervention group is comparable to the baseline date for patients in the reference cohort.

Can someone address that issue?

DR. COPELAND: I will try. I am not sure I understand 100 percent your question, but let me try, and if I miss it, please let us have a chance to ask our statistician to respond.

The patients that were enrolled in the study from the control group were done so in the

following way. A nurse associate or a research associate was given a list of UNOS I patients for the participating hospital.

She reviewed the charts. If she found that the patient had a VAD implanted, the patient was ruled out as a control patient. If the patient did not have a VAD implanted, then, the person looked through the chart to see at what point in time the patient met the entry criteria into the study, and at that time they were enrolled from that time on.

So, it was basically based upon finding all of the entry criteria in order at a given time in a historical review of the chart.

For patients who were enrolled for implantation, the item that was really the limiting factor was that they had to be transplant candidates. It usually took a minimum of 24 hours to make the patient, to go through the testing and become assured for a lot of different reasons that relate to transplant selection criteria that the patient was a transplant candidate.

So, in general, they were identified 24 hours before they had the implant. Now, there were a number of exceptions to that. Those were mostly

patients who had already been identified as transplant candidates, who came in, deteriorated rapidly either by cardiac arrest or rapid hemodynamic deterioration, and they were just sort of put into the study at the time of implant.

So, there were two ways of doing it with the ones that were implanted, and there was a consistent way of doing it with the ones who were controls. We are not making any claims about our controls. We don't even want to fight the control battle. We don't believe that the controls are matched, we are not trying to say that the controls are matched.

We do not believe that this is really, truly a controlled study. We are simply saying that this is a group of really sick patients who met the entry criteria, and they all either died or transplanted within just a few days. That is all we are saying.

DR. BLUMENSTEIN: But yet you produced Kaplan-Meier plots comparing to what you call the controls.

DR. COPELAND: Well, we drew a Kaplan-Meier survival curve for the controls and one for the implants, and I think that is a fair

thing to do.

DR. BLUMENSTEIN: That is the point, that you had to pick a date for each patient that is put onto that Kaplan-Meier plot, and then you start counting days from that date, and the picking of that date is what I think is not comparable between the groups of patients that you are putting on the Kaplan-Meier plot.

That is going to make an enormous difference in the appearance of that Kaplan-Meier plot if those dates aren't comparable for determining the same course. I don't think there is a way out of this.

DR. COPELAND: Just to explain a little bit further, when the implants were put in the study, they had to meet the criteria, so it was the day they met the criteria in both cases.

DR. BLUMENSTEIN: Well, okay, but you see the date that is chosen as the date that you start counting days is going to be very differently determined depending on whether the patient's data is getting into the Kaplan-Meier plot as a result of chart review versus as a result of observing the patient in the clinic and watching for deterioration.

For that reason, I think it is incorrect to produce those Kaplan-Meier plots. I should say Kaplan-Meier plots that compare, I think it's okay to do a Kaplan-Meier.

DR. COPELAND: Let me just ask you to forget the control curve then and--the other one because that is valid. We can show them as two separate curves if you would like, but I think they are both valid curves. They maybe shouldn't be on the same plot.

DR. BLUMENSTEIN: Precisely.

My second question--maybe the FDA people may need to be responding to this, as well--but I have heard some allusions to data from Europe. It sounds like a large amount of data from Europe. I am wondering how come we are not seeing data from Europe here.

DR. COPELAND: You are asking me?

DR. BLUMENSTEIN: I am asking whoever wants to answer.

DR. ZUCKERMAN: Just in general, we try to stick to what is in the PMA for our deliberations regarding evaluation of safety and effectiveness, and you know that in the PMA, there is a U.S. IDE trial that is described.

Earlier, you heard a European spokesman talking about a different device, and the relevance of those data to today's deliberations is not relevant.

Just like there has been some discussion of potential off-label uses of this device if it were approved in the United States. While that is interesting, what we are trying to obtain from this advisory panel is advice on whether the data contained in the PMA, i.e., the U.S. IDE trial for the labeled indication is an appropriate data set to judge safety and effectiveness.

DR. BLUMENSTEIN: I wasn't aware that the device used in Europe was different. I was under the impression it was the same device. If it is not the same device, I will shut up.

DR. COPELAND: It is the same device you have got on the table up there, but it's a different driver, it's a portable driver, and there is in your panel packet, a description of the out-of-U.S. experience, and the survival to transplant in that out-of-U.S. experience is 60 percent.

DR. BLUMENSTEIN: I was also thinking about how valuable the safety data would be to have

that much larger experience.

DR. COPELAND: Also, we are going to ask Dr. Aly Banayosy to talk a little bit about the European experience during the next public comment period, if he may do that.

DR. TRACY: Dr. Bridges.

DR. BRIDGES: Thank you very much.

I also want to compliment the investigators on the tremendous amount of work that went into this evaluation and development of the technology and their dedication to their patients, which is evident. However, I do have a couple of questions.

One question I would like to address to the Chair, Dr. Tracy. If we were to approve this device without any restrictions, what would be the labeled indications, would the so-called labeled indications that Dr. Zuckerman just referred to, would that coincide with the inclusion criteria in this PMA, or would there be some other definition of the labeled indication?

DR. TRACY: As we go through the questions that the FDA posed to us, we will be addressing whether the inclusion criteria are appropriate for the indications for use, so that is something that

this panel can discuss as we go through the individual questions, but if you have points relevant to that, then by all means make them.

DR. BRIDGES: One of my concerns, I think again a lot of this has been discussed to some degree already, and I don't want to belabor it, however, the inclusion criteria that are listed here in the PMA are extremely broad, and it is clear from Dr. Copeland's presentation that the actual criteria used for inclusion were significantly less broad or more restricted appropriately than the inclusion criteria here.

Just to review, what it states here is that a cardiac index less than 2, and one of the following, that is, CVP greater than 18 or systolic pressure less than 90, which means that if you have a cardiac index less than 2 and a systolic pressure of 88, and no evidence of right ventricular failure based on these criteria, and, in fact, you only need A or B, which is you need those two things or you need to be on two inotropes.

So, in fact, a patient that has a normal cardiac index, but is on--if I am misunderstanding, please correct me--but if you simply fulfill Criteria B, that is, you are on two inotropes, as

well as those other ones, that you eligible for transplant, et cetera, that you would fulfill the inclusion criteria, but my impression from Dr. Copeland's presentation is that clearly, those patients, the patients that I described, is not the kind of patient that was actually enrolled in the study.

Maybe Dr. Copeland could respond to that.

DR. COPELAND: Thank you for that comment because I am 100 percent in agreement with what you have said. If you look at how we came upon the criteria for this study, we borrowed heavily upon the previous Novacor IDE--sorry, I shouldn't have said Novacor--but LVAS IDE study that was organized with that company and the FDA.

Those criteria are approximately the same ones that we used in this study. We really weren't sure how this would happen and exactly which patients would get this device when we started the study, and at the end of the study, I think that I couldn't agree more with you that what we need is probably A and B together and a tighter description of the patient population as a method of coming up with the indications for this.

So, I think you are right. I apologize

for the inclusion and exclusion criteria, but we thought of those in about 1991 or '92, and we have gone through a lot of experience since then, and if I were to redesign the study, I guess I would have a much better idea of who should enter into the study and how sick they should be.

DR. BRIDGES: I think that part of our role will be to try to help define that, and I think it would be helpful if, as Dr. Yancy indicated, that we had a little bit more information on the patients that were actually included if, in fact, let's say 95 percent of the patients included actually were on two inotropes and had a cardiac index of less than 2, et cetera, then, I think it would be useful for us to know that to help to understand how to define the labeled indication, as it were, for this device.

The other question related is whether these inclusion criteria, since the stated inclusion criteria are clearly overly broad in terms of the patients who were actually enrolled in the study, is whether the inclusion criteria were different from institution to institution.

We see that the survival to transplant and the treatment success were similar between UMC,

Loyola, and LDS, but what is not in the data, unless I missed it, is whether the patient characteristics were different amongst those institutions, which might suggest, for example, that those institutions with less experience enrolled a different group of patients than the institution with the greatest experience, and that group of patients might be most relevant to the generalized use of this device.

Then, in favor of the device actually, one of the things that you did provide to Dr. Yancy, who asked for some hemodynamic information, was that you said that 38 percent of the patients had CVPs greater than 18, and only 65.8 percent of those survived to transplant, which would imply that 62 percent of the patients had CVPs less than or equal to 18, and that a higher percentage of them actually survived to transplant, which would suggest that perhaps this device could have an application for patients who don't have right heart failure, and it might very well be that this device, that biventricular support may be the way to go even in patients who we might otherwise think are candidates for left ventricular support only.

So, by looking at the data more carefully

in terms of stratifying it both in terms of hemodynamics, body surface area, for example, or pulmonary artery pressure, CVP, we might be able to define patient subsets that do particularly well with this therapy, and we might discover that the patients who we think aren't going to do that well, are actually doing better than we thought they might be, which is why I think it would be important to get that information.

DR. COPELAND: I am in complete agreement again with what you say. What we are trying to do is save lives, and the way we are identifying the people to be saved is by how sick they are, and it is not always based upon right heart failure. Sometimes it is based upon a huge amount of inotropic support.

Could we have P38, please.

[Slide.]

This is just a reiteration of the presentation, and it does show the large amount of inotropic support greater than or equal to three drugs for the core patients as compared to the control, so you can see these people are on lots and lots of inotropic support.

So, I think that, you know, they are a

very sick group of patients, and they do have indications that extend well beyond right heart failure, and getting them off inotropes, allowing their organs to recover, getting them off vasoconstrictors, those kinds of things are real issues in these patients.

If you would like, we could have Dr. Long and Dembitsky comment on indications in their institutions as compared to ours, if that would be helpful to the panel.

DR. TRACY: That's fine, if they would.

DR. COPELAND: We will have Dr. Long first and then Dr. Dembitsky.

DR. LONG: Simply put, we wouldn't have much different indication than they would have at Tucson.

DR. DEMBITSKY: Well, we are constrained in San Diego by the financial liabilities in implant technology that we can't be reimbursed for, so we are very careful about applying it.

So, we only apply it when we think it is absolutely necessary, and I must say we have used biventricular devices when it would have been better to use the other device for that reason, because it would destroy our program.

However, there are certain niches where the retained heart continues to be a liability, where there is no substitute, and just to reiterate that, if you have a retained rejected heart, that is a problem. If you can take the rejected heart out that you have transplanted and replace it with a device, stop immunosuppression, that is good for the patient.

If you have persistent arrhythmias that are a liability for biventricular support as opposed to total artificial heart support, that is a liability, the retained heart. In addition to that, retained sometimes a clot and artificial valves, that sometimes those patients would be better. That is in addition to the systemic problems that some of these patients have, which we addressed before.

DR. TRACY: Anything else, Dr. Bridges?

DR. BRIDGES: No. I just want to reiterate, though, I think it would be nice, though, if we did have an actual breakdown of what the patient characteristics were. I mean we have got the whole group, but it might be helpful for us to see what those criteria were at the other two institutions separated from UMC.

DR. TRACY: Do any of the other panel members have additional questions to ask at this time of the sponsor?

If not, then, let's break for a 15-minute break and resume here at five of 4:00.

[Break.]

DR. TRACY: We still have a good deal of work left to do here this afternoon. The next order of business is for the panel members to review and discuss the questions that are posed to us by the FDA regarding the product.

I will ask Ms. Wood to read the FDA questions to the panel.

MS. WOOD: The first question is: Please discuss whether there is reasonable assurance that the results from UMC can be generalized to all transplant centers.

DR. TRACY: I think we will try to discuss each of these. There are several questions, but we will try to discuss each of these, the point here being that there were five participating centers in the trial, but 60 percent of them came from a single center, so of the 95 devices that were implanted, 68 percent were implanted at UMC.

So, the question to the panel is whether

it is reasonable to assume that the results at UMC can be generalized to all transplant centers.

I think if I can try to summarize what we have seen and the discussion a little bit, everybody did raise some concern about that. I think that the panel had some assurance that the initial concern about financial conflict of interest, at least to my mind, has been reasonably answered.

I think it is a matter more of happenstance and availability that there is a disproportionate distribution from the centers, and I think that is a question that you have to ask of any study where there is a majority of cases being done at one center compared to the others.

However, I believe the technology, we have heard from several surgeons the technology or the techniques of implant would be the same at different centers, so from a technical standpoint, I think there would be agreement that the outcomes would be similar at different centers in the hands of a technically adept surgeon.

Does that summarize the panel's feeling on this? Okay.

MS. WOOD: Question 2. Please discuss

whether the safety parameter results of the clinical trial provide reasonable assurance of safety in the intended population. Accordingly, does any class of adverse events, such as infection, bleeding, or neurological event, raise concerns clinically for a ventricular assist device in bridge-to-transplant patients. If so, what warning should be included in the labeling?

DR. TRACY: Again, to take a stab at the discussions, a summarization of the discussion, it is important to think of this device as simply what it is, a bridge to transplant, not a bridge to improvement in clinical status. It is obviously a one-time deal. The heart is out of the chest and there is no putting it back in.

So, the question is compared to nothing else, is this thing safe in terms of infection, bleeding, neurologic events. It is an extremely difficult patient population.

My impression from the data and from the comments I am hearing from the panel is that the level of adverse events is acceptable in this highly sick population, but I would like to hear if there is any other comments that the panel would like to make regarding this. Mitch.

DR. KRUCOFF: I certainly don't think we can call this a data set that provides reasonable assurance of safety. I think we have a profile. I don't know how in the world we would interpret what's the patients, what's the device, or what the safety profile, what even the appropriate patients are based on this data.

DR. TRACY: Dr. Aziz.

DR. AZIZ: I think in terms of device malfunction, I think you could say it is safe. They have only had one malfunction in all the patients that were done. I think targeting the issue of neurological events, I think the rates are not higher than other VAD devices, whether it be UNIVAD or BiVAD that are out there.

In terms of device malfunction or dysfunction, I think it is very good, but if you are talking about the criteria of use, I think that is a different issue.

DR. TRACY: I think it is one of the areas where we suffer from a lack of a comparison group, so the best that we can do is look at other types of devices, and I think the data presented does not show this to be way out of line with other types of devices.

Is that a fair way of putting that? Dr. Yancy.

DR. YANCY: I think that is the threshold, that it meets other devices, but I think we ought to also acknowledge that, in general, this complication rate is still unacceptably high, and we need to encourage other providers, other innovators that we should work towards reducing these rates, and that in our post-marketing survey, if we go forward with the label, we ought to follow these events very carefully, as well.

DR. ZUCKERMAN: Dr. Tracy, could you just clarify for the record then, is it the majority of the panel members who believe that there is reasonable assurance of safety and Dr. Krucoff's opinion is a minority opinion?

DR. TRACY: Let me clarify that. Dr. Yancy, when you say this is unacceptably high, I think that is more of--

DR. YANCY: A generic statement.

DR. TRACY: It is a statement that nobody likes this high level of complications, however, relative to this particular situation, this particular device, and the status of technology at this point, it is not unacceptably unsafe.

DR. YANCY: It has met the current thresholds, yes.

DR. TRACY: My sense, and I will give Dr. Weinberger a chance here in a second, my sense is that the majority opinion would be that given the parameters of the technology, that it is safe.

DR. WEINBERGER: I think what I am hearing from you and what I think, and certainly that was the underlying question from Dr. Hirshfeld earlier, this is not a safe device, this is not something that any of us would subject ourselves to unless we were dying, and I think that the only way to consider this device as safe is in the context of the fact that these people have essentially no other therapy available.

So, it is safe if you are saying that the benefits outweigh the risks. If that is what safe means, then, we are sort of over the line between safety and efficacy, but if that is how we interpret safety, as being a net benefit to the patient, I think this likely has net benefit to the patient, but it is certainly not safe in any absolute sense, I wouldn't subject myself to a 20 percent stroke rate risk for no other reason.

DR. TRACY: Does that clarify things? Dr.

Ferguson.

DR. FERGUSON: Well, I take a little minority opinion on that, because I think the context--if I am incorrect, you can correct me--but the context here is whether the device itself is safe.

If they came in here with 25 or 30 diaphragm perforations, then, I would say the device is not safe, but putting it in the clinical arena, I think it is safer than most of the devices--well, all of the devices that are out there right now.

DR. ZUCKERMAN: That's fine.

DR. TRACY: Okay.

MS. WOOD: Question 3. Please discuss whether you believe that the CardioWest TAH is efficacious as a bridge-to-transplant device for patients with biventricular failure.

DR. TRACY: The background on this, the CardioWest TAH has a survival to transplant of 80 percent for the core device group and a 75 percent for the entire device group.

I am not sure what slide this CardioWest TAH survival profile would be on, the panel has that on your questions, showing the overall

survival rate at 6, 12, and 24 months, and mean time to death, et cetera.

The question being is the device efficacious as a bridge-to-transplant device for patients with biventricular failure. Again, to try to summarize the complex discussions that we have had, it is only that, a bridge to transplant, and I think it has demonstrated that it is efficacious as a bridge to transplant.

Agreement?

DR. KRUCOFF: I take the minority position.

DR. TRACY: Any comments you want to make, Mitch?

DR. KRUCOFF: I don't want to be a broken record. I just think there is absolutely no way from this data set to understand relative to either the natural history or the impact of the device who these patients are or where they would end up from the data.

DR. TRACY: So, the majority opinion is that it has been shown to be efficacious. Minority is again suffering from the lack of a control group that is hard to make that--I am sorry, Dr. Yancy.

DR. YANCY: May I raise one question? I

accept the notion of bridge to transplant without too much difficulty. Do we have to accept the statement as posted, that is, with biventricular failure? Can we modify that statement, or do we vote as it is, as it stands, i.e., if we put advanced heart failure as opposed to biventricular failure?

MS. WOOD: You will have a chance to do that when we vote for approval or disapproval.

DR. TRACY: Okay.

MS. WOOD: Do the indications for use adequately define the patient population studied and for which the device will be marketed?

DR. TRACY: I think this is the tricky part.

MR. MORTON: Let's review the indications for use.

DR. TRACY: I think the requested indication for use simply states as an in-hospital bridge to transplantation in cardiac transplant candidates at imminent risk of death due to irreversible biventricular failure.

So, that then is compared with the entry criteria to the study which were first devised in I guess the 1990s, and that is in the sponsor's P30

slide that discusses the various cardiac index, systolic less than or equal to 90, CVP greater than or equal to 18, and two of the following requirements for various inotropes or intra-aortic balloon pump, which then is contrasted with the proposed or the speculated group of TAH candidates, which was Slide P88, which listed a variety of different clinical scenarios that might lead one to be in these categories in the first place including RV failure, LV thrombus, refractory arrhythmias, prosthetic aortic valve, et cetera.

So, there is a little bit of ambiguity here. The original indication that is being requested here is bridge to transplant in imminent risk of death in biventricular failure, yet, the speculated patients one might conceive as not having biventricular failure although the assurance from Dr. Copeland and the sponsor is that the overwhelming majority of the patients did, in fact, meet multiple entry criteria. They were not one from Column A, one from Column B, they were one or two from Column A and one or two from Column B.

So, I think what might ease the situation is when we start discussing labeling, that we ask for something on the order, if we get that far, of

a clearer definition of who the patients were included in the study.

But I think it is something that we are obviously all wrestling with. My feeling would be that the indication is broad enough to be appropriate, but I can see where there might be some argument regarding the biventricular.

Dr. Hirshfeld.

DR. HIRSHFELD: I think the root cause of the problem is that we will never ever be able to develop a rigorous definition of biventricular failure.

Certainly, with the data set that we have, we are not going to be able to develop any criteria that distinguish between the patient who would do just fine with an LVAD and the patient who would really derive true incremental benefit from this device over what they would get with an LVAD.

So, I think if we get to that point, we are going to have to figure out a way to deal with the fact that I don't think we can rigorously define what that indication is.

DR. TRACY: Dr. White.

DR. WHITE: I think I heard them say distinctly that the only patients that would be

candidates for this device would be not a candidate for an LVAD. I don't think it is an issue of either an LVAD or this device.

I think if the patients are candidates for LVADs, they should get LVADs. This device doesn't compete with that population because of the nature of the biventricular disease. I think that is what I heard.

DR. HIRSHFELD: Well, I am not convinced that the criteria that were used for eligibility, which mainly derived from high right-sided filling pressures and low cardiac output, necessarily definitely specified that that is true by ventricular failure, as we all know.

I wouldn't be surprised if in that data set, there are patients who might have done just fine with an LVAD. We will never know because the trial wasn't conducted, and then we had to rely on the clinical intuition of the people who were taking care of the patients, but I just don't think we can say that we know who has a condition that requires biventricular, in this case, replacement as opposed to people who would actually perk up quite nicely on the LVAD alone.

DR. WHITE: But I think the criteria in

the trial were that they had to not be candidates for LVADs.

DR. HIRSHFELD: Right, but what made them not a candidate was not defined in terms of criteria that we could write down and say these are reasons why you are not a candidate for an LVAD.

DR. TRACY: Dr. Ferguson.

DR. FERGUSON: I just wanted to add that under the clinical summary, on page 12, which gives us the inclusion and exclusion criteria, need to be looked at carefully in light of what we are talking about now, because there is a pretty bad disconnect between I think what I heard the panel discussing and what those criteria are, and that was brought up earlier, that these were developed 10 years ago.

DR. TRACY: Dr. Kato, did you have a comment you wanted to make?

DR. KATO: Yes, I would agree. The exclusion criteria here just says that if any LVAD was used, then, the patient was excluded from it, not that they were not a candidate for an LVAD.

DR. TRACY: I agree with you, Dr. White, that that was the statement that was made. My understanding of the statement that was made was these patients were not candidates for LVADs

because of their biventricular disease.

Now, the exclusion criteria go back to the historic problem here, that these criteria were derived 10, 12, more than that, years ago, and were stated as relevant to the technology that was available at that time, but I think on a clinical basis, it was clear that these were not, in the operators' minds, candidates for LVAD.

I don't think that was solely based on the written exclusion criteria.

Actually, we have sort of merged question (a) and (b) here, 4(a) and (b), which is: Does the labeling adequately describe the patients which would require BiVAD support as opposed to LVAD support?

I am getting the sense that the labeling does not specifically address that it is based on clinical criteria that appeared to be, I am not sure generally acceptable, but appear at least in the operators' minds to be clear enough who is and who isn't a candidate for LVAD versus requiring BiVAD support.

I think it gets back to the experience of the operator and requiring a pretty clear definition of who and who was not in the study,

which should be incorporated into the labeling, I would think, better than it is stated currently. I am not sure I can take it much further than that.

DR. YANCY: I would support the direction you are going, and I would likewise support what Dr. White just alluded to, and that is that perhaps in a very easy way, the statement that already appears as an indication should just simply include the proviso of not an LVAD candidate or some other language that captures that, because it seems as if, in practice, that is the way that this was applied, and that makes some of our angst a little bit easier.

DR. KRUCOFF: Cindy, that was a phrase that was used when the retained heart is a liability, that again capturing the flavor of this, I think the spirit of this is doable. Ultimately, when you get down to who are the patients that we have data on, and how are they going to behave differently than what indications for use that follow the spirit of this take us that we do have a disconnect. We have a very major disconnect, but ultimately, that goes back to our ability to determine safety and efficacy in the first place.

DR. HIRSHFELD: Cindy, not to prolong

this, despite the fact that I am nihilistic about the data that enable us to identify who is a candidate for an LVAD and who is a candidate for a total artificial heart, I don't think necessarily that we or FDA needs to be worried about making that distinction. I think that is a distinction of clinical judgment.

I think we would be going beyond the bounds of clinical judgment to put in a criterion that said you have to not be an LVAD candidate to be eligible to receive this device. I think that is something where we need to leave that to the clinical judgment of the physicians caring for the patient.

DR. ZUCKERMAN: I think that is correct, Dr. Hirshfeld, but could you look more specifically at page 4 of the labeling, which lists the current indications for use. It is Section 2.0.

DR. HIRSHFELD: I think the only weakness in that statement is that I don't think we could define biventricular failure. I think the real criterion is imminent risk of death, and that if the patient is at imminent risk of death, that it is justifiable to implant some sort of a mechanical assist device in the patient including this one.

DR. TRACY: We may be skirting it a little bit, though, because the imminent risk of death from a brain tumor, I mean I don't want to get crazy here, but I mean the implication is it is imminent risk of death from heart failure, and how much do we want to pin them down to you have to satisfy criteria of biventricular failure when we are all having a hard time understanding how you specifically make that diagnosis, or do we intentionally leave it a little bit ambiguous, but clearly state somewhere in the labeling who these patients were.

That leaves it open for clinical interpretation on the operator's clinical judgment of the patient's prognosis.

DR. AZIZ: That statement they have I think covers that, doesn't it? It says from non-reversible biventricular failure, but it doesn't set the criteria, and leaves it to the clinician to decide that.

DR. KRUCOFF: There is only one contraindication to VAD, might be an artificial valve, you might not have irreversible biventricular failure.

DR. AZIZ: That would be a

contraindication to an LVAD. I think you would have those other criteria, because you could have, let's say, a VSD or something that resulted in biventricular failure, or you get a ruptured LV or something.

DR. TRACY: Right, or arrhythmia for that matter may not require biventricular failure. I think in a way it is really dependent on the operator to determine exactly what that means. It might be appropriate to state "or the retained heart is otherwise at risk of death."

DR. KRUCOFF: I think if you want to license the spirit of the gadget, irreversible biventricular failure, other contraindication to LVAD, or liability of the retained heart are the three sort of rubrics that cover the ground.

It is just that ultimately, what we are doing is licensing something that is way beyond.

DR. TRACY: My question, I am a little concerned about putting that directly in the indications for use since that specific population was not necessarily studied in large enough extent to make those statements. I don't know that there is enough arrhythmia patients in there to make that statement.

I think that leaving it rather broad might be the appropriate way, but clearly stating who the patients were is in the labeling.

Dr. Maisel.

DR. MAISEL: I agree. I am comfortable with the term "imminent death from non-reversible biventricular failure."

I am uncomfortable with the idea of starting to spell out all the other reasons that we haven't seen data for, and if a physician wants to implant the device off label, I don't know that that is our purview to discuss, but it seems like the data we have seen today, in my opinion, support the non-reversible biventricular failure, and not other things.

DR. BRIDGES: Another possibility would be to actually add an indication and say irreversible biventricular failure or severe heart failure, for example, that is not amenable or life-threatening, reversible heart failure, not necessarily biventricular, in a patient who is not a candidate for univentricular support device.

I don't know if you want to go there, but I mean that would capture those other--because my concern with just saying biventricular failure is

that you exclude those patients who are candidates for the device for all those other reasons, for example, you have got univentricular failure, but you have got a VSD, but if you say imminent risk of death with severe cardiac dysfunction and not a candidate for one of these other devices. That is just another way of doing it.

DR. TRACY: Does the panel think we have enough data on the specific other patients to remove the word "biventricular," just say "ventricular failure who are not otherwise considered candidates for other assist devices," do we have the data to support that indication?

Dr. Ferguson.

DR. FERGUSON: I come down on the side that votes to retain just exactly what is here. If we begin to define what can be operated upon and the device used, then, that is a slippery slope, I think.

DR. TRACY: Dr. White.

DR. WHITE: I would second that, I agree with Dr. Ferguson and Dr. Maisel. I would leave it at biventricular.

DR. TRACY: An unofficial quick poll. Retain the word "biventricular."

Dr. Yancy?

DR. YANCY: I would prefer the word "advanced" in lieu of "biventricular," since that is what it was, but I wouldn't object if you keep it.

DR. TRACY: Dr. White, I think you were biventricular. Dr. Hirshfeld, biventricular. Dr. Ferguson, biventricular. Dr. Krucoff.

DR. KRUCOFF: Abstain.

DR. TRACY: Abstain.

Dr. Bridges.

DR. BRIDGES: I think it is okay to leave it as it is, although I think that it could potentially be misinterpreted as an inappropriate application of the technology in a patient who doesn't have biventricular failure, but clearly has another indication for the device.

DR. TRACY: Dr. Aziz, okay.

I think that the consensus is leaving the word "biventricular" alone is appropriate.

I believe that we have discussed Section (b) of Question 4.

DR. ZUCKERMAN: Could we just clarify that. This has been a major issue that the panel has struggled with today, and generally, we would

like to have some discussion of that in the summary of clinical study, which is Section 6.0. Given the problems with the clinical study, choice of patient population, et cetera, is this the type of summary that the panel is looking for, or do we have to perhaps stress certain other things?

DR. TRACY: You are referring to the labeling section in the panel packet?

DR. ZUCKERMAN: That's right.

DR. TRACY: In 6.0. I think that there is consensus, I believe that this is not adequately descriptive of the patients who were involved in the study, that we would like there to be more details provided regarding who exactly was included in the study. This is fairly brief, I believe.

Dr. Krucoff.

DR. KRUCOFF: Cindy, I think one other thing that has come up, I think pretty repeatedly, would be if the data could be structured, so that outcomes were understandable, for instance, more on the basis of measures indicating biventricular failure, so elevated pulmonary pressures, liver function, you know, if the clinical summary actually structured the data to the issue of biventricular dysfunction, that might be helpful.

DR. TRACY: Some more detail than perhaps trying to orient it, so that there is a closer correlation with the hemodynamic or other clinical parameters at entry.

DR. ZUCKERMAN: Okay. And the other question that comes up is as presently written, the summary of clinical study does contain p-values that compare the experimental arm to the control group.

Is that a valid approach, or should the control group and p-values be deleted, and just the one-arm study results be described with confidence intervals?

DR. BLUMENSTEIN: I am very much against any p-values comparing a reference to an intervention in this setting, and I think that even putting a reference group and the intervention group on the same Kaplan-Meier curve isn't valid either.

DR. TRACY: I think that the consensus, the feeling is that the sponsor was sort of stuck with that control, that we don't feel is the appropriate body against which to compare this thing, so reporting p-values probably is not relevant, and I think we would prefer seeing a

greater detailed clinical explanation of patients.

DR. BLUMENSTEIN: And also not to call it a control group, because it's not a control group.

DR. TRACY: Right.

DR. KRUCOFF: I think it would be informative to, in a modern era, take an approach to an historical structured chart review amongst, say, participating institutions, and actually try and learn something from patients who were not treated with this device as maybe a little better basis.

Again, to me, that would just illuminate a little bit more what the real safety and efficacy profile would be in a comparable patient population.

DR. TRACY: Does that answer the question the FDA posed?

DR. ZUCKERMAN: I think we have enough information now to rewrite the label, yes.

MS. WOOD: Are there any additional warnings, precautions, or contraindications that you think should be included in the labeling to assist practitioners in determining the need for biventricular support?

DR. TRACY: To direct the panel,

Contraindication Section is 3.0, CardioWest TAH's contraindication for use in patients with body surface area less than 1.7 meter-squared.

That is the only contraindication that is stated there. I guess the AP diameter falls out as a contraindication, and I thought that small people could get the device if they had large hearts.

Did I miss something or does that come from the historical exclusion criteria?

DR. ZUCKERMAN: In writing a contraindication, generally, we want to have data, such that we can support stating that this should never be done, so although people have stated this or that, are there data that are strong enough, such that you want another contraindication statement that says for this patient or that patient, the device should never be used?

DR. TRACY: Dr. White.

DR. WHITE: I think what they intend to say is that the absolute contraindication is do not put the device in somebody in whom it doesn't fit, and I think then we go on about trying to help the clinician who is reading this try to understand who it might not fit in, so telling people that small

body habit is less than 1.7, AP diameter less than such and such would all be parameters that would indicate that it well might not fit.

I think if that criteria was used for the trial, I think I would base my exclusion on that criteria, but the wording might be simply it is absolutely contraindicated in people in whom it won't fit, and then to help people try to understand who that population might be.

That then leaves you the wiggle room to, if you believe the device will fit in experienced hands, as Dr. Copeland has told us that he can tell or thinks he can tell who it will fit in, then, it gives him some room to do that as opposed to just arbitrarily taking everybody who is less than 5 foot 2 out of the pool that can get this device.

DR. FERGUSON: I agree very much with this. This is sort of a bald statement without explanation, and I think it needs to be put in this in terms that Chris said.

DR. TRACY: I think that is probably more reasonable because if we go back to, as faulty as they may be, it wasn't one of the original exclusion criteria, the body surface area, however, I assume that came from clinical experience, and I

think that stating if it won't fit, don't use it, but then there might be some better way of descriptively saying in whom it wouldn't fit, it can be included.

DR. MAISEL: Is the presence of a VAD a contraindication, an LVAD or a BiVAD?

DR. AZIZ: Obviously, in this trial, that was an exclusion criteria. I think obviously, the European experience, there are patients I think who you will put a VAD in, even a BiVAD, that are doing poorly, and if you catch them early, so I would imagine that in clinical practice, this will be put in patients who have a VAD and who failed, and that is a logical step.

DR. TRACY: To go on to the Warnings, in Section 4.0, and they are listed there. There are 10 warnings that are listed on page 5, if you want to take a second to look at them.

They should only be used by people who know what they are doing. They should only be used once. Hasn't been used in pregnant women. People shouldn't have MRIs. Safety and effectiveness in populations other than those of idiopathic and ischemic cardiomyopathies has not been established.

Don't use if the artificial ventricles

don't fit. Don't let catheters near the inflow valves of the TAH. There is potential for air embolism, de-air the artificial ventricles to minimize the possibility of air inadvertently entering the device. Don't allow external drivelines to be kinked. Reduction of maximum stroke volume on the external console's monitoring computer to blow 50 mm may indicate a failure of one of the diaphragms in the artificial ventricle of the TAH.

Mitch.

DR. KRUCOFF: At the risk of being a persistent minority, I would be inclined to start No. 5 by saying, "Safety and effectiveness of this device has been extrapolated from an observational study, not randomized clinical trials and is not established outside"--at least somewhere in here, to let people be aware that the data on which we are basing safety and effectiveness is very unusual.

DR. TRACY: I think even though that may be true, the people who were included here were idiopathic and ischemic cardiomyopathy, even though it is not a randomized, controlled trial. In fact, they were people with ischemic and idiopathic

cardiopathy.

I think I agree with you that there needs to be more definition of who was in the study. I don't think it comes in the category of a warning, but I think you are right, that it needs to be stated in there somewhere much more clearly than it is.

Dr. Kato.

DR. KATO: I would like to see a statement that this device should only be used at centers with heart transplant programs.

DR. TRACY: Should?

DR. KATO: Should only be used at programs with active heart transplant programs. The reason why is because I think we have seen that there is enough complexity to it that having this device available to the open market might cause a number of problems in terms of implant criteria, as well as complications.

DR. ZUCKERMAN: The actual ability to state that on a label may be somewhat questionable. I do think the label will capture the need for appropriate training and use at a highly experienced center, but we will investigate that point, Dr. Kato.

DR. TRACY: Dr. Hirshfeld.

DR. HIRSHFELD: I wonder if it is appropriate to put in the warnings that there is a requirement for a very careful antiplatelet and antithrombotic therapy and monitoring in a device that has four mechanical valves.

DR. TRACY: I think that would be very appropriate.

DR. WHITE: That just reminds me, then, obviously, a contraindication would be a patient who could not be anticoagulated.

DR. TRACY: That would be true.

DR. WHITE: That might be an absolute contraindication if they could not take warfarin for whatever reason, then, you wouldn't want to put this device in.

DR. TRACY: Warfarin or some other--

DR. WHITE: The question is, is it possible to manage this device without warfarin, is it possible to manage this device on antiplatelet therapy only?

DR. AZIZ: Could you put this into patients who have a history of HITs?

DR. WHITE: I am just saying if you have a patient you know you can't anticoagulate, and there

are people that cannot be anticoagulated for other bleeding risks, then, they would not be a candidate for this device because you would run into that brick wall, so that perhaps ought to go under the contraindications.

DR. AZIZ: In the same vein, if somebody has a prior history of HITs or heparin-induced thrombocytopenia, should that be included?

MR. MORTON: Here is a point that I have, actually, although this device looks very different and has a different indication from a lot of other devices that have come before the panel and been PMA approved, really, we are struggling with just something like valves, which are put in every day, and so would we not want our labeling to be somewhat consistent with labeling for those devices which are out there, and I don't recall a contraindication for coumadin in valves.

DR. WHITE: As one who never reads the label, but we would never put a metal valve in a mitral position in a patient who could not be anticoagulated, so we would use alternative tools. So, if there is an absolute requirement for warfarin here, then, I think that that would be a contraindication.

DR. TRACY: I guess we need the FDA to advise us. I agree that the device has artificial valves and that the labeling, in terms of the anticoagulation, should probably be reflective in some way of that.

I think the person would need to be anticoagulated either with warfarin or with heparin or low-molecular weight heparin.

DR. YANCY: What is a warning versus a contraindication?

DR. TRACY: Contraindication is stronger meaning don't do it in someone who can't have anticoagulation.

DR. YANCY: So, where does this anticoagulation part go?

DR. TRACY: I would think it would be a contraindication myself.

DR. MAISEL: We can do something more generic like don't implant it in someone who cannot receive adequate anticoagulation.

DR. ZUCKERMAN: That's right, and that is similar to, for example, what the coronary stent labels say in their Contraindication Section. I mean if it's an obvious part of the treatment where you are headed for disaster if you can't use the

adjunctive pharmacotherapy, then, it is generally a contraindication.

DR. TRACY: So, in terms of a contraindication, then, we probably do need to add do not implant this device in patients who cannot receive anticoagulation, and as part of the warning, just indicate that close monitoring of anticoagulation is required during follow-up.

DR. HIRSHFELD: And the protocol that is used involves monitoring the efficacy of antiplatelet therapy, as well as antithrombotic therapy. That is what is specified in the protocol so far, so the investigators are very careful to monitor the efficacy of their antiplatelet therapy in addition to their antithrombotic therapy.

DR. TRACY: So, the language should reflect that.

Then, the Precaution Section, measures should be taken to prevent infection or sepsis. Use strict antiseptic technique. Orthografts must be pre-clotted before use. When closing the chest, a reduction in device output may indicate inflow obstruction, reposition the artificial ventricles by anchoring to a rib or moving into the pleural space.

Do not use antifibrinolytic like Amicar or aprotinin with an active clotting agent like FEIBA. Use only water soluble antiseptic cleaners around the exit site, ointments may delay tissue ingrowth into the driveline conduits. Each external console contains a primary and backup controller and an additional external console should be available for use.

A sudden reduction in CardioWest TAH flow may be due to a kink in the pneumatic drivelines or some inflow obstruction to the CardioWest TAH, such as tamponade, defibrillation, or CPR will not be effective.

These sound to me all like hard-learned lessons.

Dr. Ferguson has a point regarding the pre-clotted.

DR. FERGUSON: A point of clarification. I thought you said that the outflow grafts were pre-clotted already, or I misunderstood.

DR. COPELAND: As they currently exist, they have to be pre-clotted at the time of implantation.

DR. TRACY: Any other comments from the panel on this part? Okay.

MS. WOOD: Please comment on the adequacy of the proposed physician training plan as described in the panel package, Section 7 of the Clinical Summary.

DR. TRACY: The proposed physician training program, SynCardia has developed a training manual to be used in all new centers with transplant teams who will be implanting the CardioWest artificial heart. Based on training experience to date, SynCardia proposes that minimally, the following elements will be completed and documented before the first human implant at any center.

Equipment training. SynCardia will provide a clinical specialist and an engineer to review the device specifications, operation of the console, functional expectations of the artificial heart. The review will include summary of clinical experience with the device, review of the instructions for use, and Operators Manual.

The overview will be provided to the entire team of individuals who will be implanting, maintaining, or servicing the system. The team will set up a complete TAH system using a mock circulation unit for practice.

Animal-experienced surgeons and their team at each center will perform a minimum of 2 implants on an animal model under the direct supervision of SynCardia. Animal experience is particularly helpful to technicians who will later be responsible for maintaining the equipment on patients, therefore, all technical support personnel should be included in this portion of training.

Surgical proctors. SynCardia will maintain Centers of Excellence where surgeons who request it may view an implantation of the CardioWest TAH. Further proctors will be available for surgical teams during their first case.

So, a combination of training on-site for all involved personnel, animal implant, and the availability of a proctor either to come to your center or you to go to their center.

DR. WEINBERGER: I think that this should be a mandate that the first case be proctored, and not just make it up to the surgeon to decide whether or not he wants a proctor around. I mean here it says a surgeon will be available if requested, but my understanding was that the first case would have to be overseen.

DR. TRACY: I would think that that would be an appropriate level of mandating proctorship for at least the first case.

Agreement from the panel on that? Okay.

DR. YANCY: Just one additional question. The section is labeled "Proposed Physician Training Program," but I am going to assume that nurses are involved in managing the console. Is that not correct, because if it is, there should be some educational component there, as well.

DR. TRACY: I think they do specify that all members of the team involved should be involved in the training, and maybe that section should be relabeled "Proposed Team Training Program" or "Proposed Implant Team Training Program," so that it does create the expectation in everybody's mind that the entire team be involved in the training.

Dr. Hirshfeld.

DR. HIRSHFELD: Related to this, maybe I should ask the more experienced people and Dr. Zuckerman, is it appropriate to specify qualifications for the entire team that would be authorized to use this device?

In other words, we are talking about this device being used only at experienced transplant

centers by experienced transplant surgeons and experienced heart failure physicians, but I don't see that anywhere in any of the documentation about the eligibility to use the device.

Is that something that FDA doesn't have the purview over, or is that something that can and should be specified?

DR. ZUCKERMAN: We can consider putting that in the label, if that is the advice of the advisory panel.

DR. TRACY: My impression, though, is that presumably no transplant team is going to open its door without the expectation that they can provide good care, and I think you don't necessarily want to restrict this only to established centers. It is conceivable that somebody would want to open a new transplant center and have therefore not an experienced team, but experienced individuals. I wouldn't want to tie any new center's hands too much by specifying that the team be experienced.

They may want to purchase this as their first major assist device in that new center. I think that the expectation is that the transplant team would have the wherewithal to perform this type of procedure.

DR. HIRSHFELD: I was just raising the question as to whether that should be specified.

MS. WOOD: No. 6. Based on the clinical data provided in the panel pack, please comment on the design of the post-market approval study proposed by the sponsor. Is follow-up of 1 year post-transplant with data collection for adverse events appropriate?

DR. TRACY: I think the quickest summary of the proposed post-market surveillance is Slide P91 from the sponsor, where they propose a follow-up on the currently enrolled study patients plus 50 additional U.S. patients to demonstrate generalizability, plus less than 10 percent from any one center, plus adverse events captured during implant period, survival to transplant, and 1 year follow-up.

I am not sure who the 1 year follow-up is on, all patients currently in the cohort plus the 50 additional patients?

How much post-market surveillance do we want?

Dr. Weinberger.

DR. WEINBERGER: I thought we had at least agreed that we wanted post-market surveillance on

all patients, not just the first 50. That is one important point. I think that this is going to be a rare enough event, we are talking about a couple hundred patients, so we would like to assure ourselves that the centers achieve bridge-to-transplant rates that are comparable to what the sponsor has shown.

So, I would like to get a post-market follow-up on basically all patients for the first year.

DR. TRACY: Dr. Krucoff.

DR. KRUCOFF: Just as a reality check to the panel, I think it is worth recognizing completely independently from the sponsor that the success in getting any post-market data, once you get out of the gate, even when post-market conditions are applied is poor.

So, we can create any proviso you want. What will actually emerge is not going to be well controlled.

DR. TRACY: I think the other issue is the rigor of the post-market surveillance, whether it's a registry or whether there is--

DR. WEINBERGER: Bram, is that true you don't have any leverage to make sure you get

post-market at some rate of follow-up?

DR. ZUCKERMAN: Not necessarily. Again, the ability to do this in this field has been reasonable, so what the agency really needs from the advisory panel are what are realistic goals in a post-approval, for example, the agency can't necessarily mandate follow-up on every patient implanted post-approval unless we have a sufficient justification for it.

For example, Dr. Weinberger, are you asking that we reconsider an appropriate sample size, such that with X number of patients followed post-approval, we will have sufficient safety data with appropriate confidence intervals. Then, we can reconsider with the sponsor what the sample size is. It may not be 50 patients, but we can't just ask for things carte blanche periapproval, as conditions of approval.

DR. WEINBERGER: I didn't mean to imply that we should ask for indefinite follow-up of all patients with implants.

I agree with you that if we can come up, based upon statistical considerations, with what should be a pretty tight estimate or a pretty reasonable way of estimating what it would take to

demonstrate comparable safety results once it is released to the public, once it is released to the general medical public, I think that would be a reasonable way to go.

The primary endpoints of this device are really bridge to transplant, so we don't need one-year follow-up on every patient. We need to know when each individual patient who gets a device gets the transplant, whether there have been any untoward events or whether they died. That is really what this device is about. This is not a permanent device.

DR. TRACY: I think that that idea that Dr. Hirshfeld raised on a couple of occasions, is there some other reason why there is increased complication at the time of transplant, so maybe defining a period of time from implant of the device through 30 days post-transplant or 60 days post-transplant on some cohort of patients, new patients, in addition to continuing following the original group that was included in this study might make some sense just to try to capture acute adverse events and anything that might pop up later.

DR. FERGUSON: The number is 50, but they

want to follow out to one year, I think we ought to talk about that. I think there is reason to follow a cohort, I don't know what size it is going to be, but a cohort of patients to one year out from transplant.

DR. BLUMENSTEIN: Absolutely. I can't see any less than that.

DR. FERGUSON: I thought somebody said just follow them for a short period of time since the device is already gone. You don't agree with that.

DR. WEINBERGER: No. I think that we sort of agreed that once patients get out to 30 to 60 days post-transplant, we believe, I mean we have a pretty good idea that they have rejoined their cohorts.

Maybe we need a little data to demonstrate that, but I don't think that we can mandate basically the scientific rigor that we would have liked pre-release, as well.

DR. TRACY: Dr. Maisel.

DR. MAISEL: I am concerned about the applicability in the real world, and I think that can be answered by survival to transplant. I think that number would give us a good idea of how

effective this device is in the real world.

I am also concerned about the number of device malfunctions and complications, and I think there is a very real chance that there will be a flurry or a steady stream of events flowing into the FDA, and they will be uninterpretable without knowing the denominator, and I think that is another important reason for trying to get a handle on the number of patients with the device.

DR. BLUMENSTEIN: I think when I said a year following transplant, that doesn't really have to be that burdensome, because the main issue for going out a year would be survival, and there could be two different phases of follow-up post-transplant - a detail phase to find out complications from the transplant itself, that might be related to the use of the device, and then a longer, just to survival, which could be a lot more passive for long-term effects.

DR. FERGUSON: I don't want to prolong this, but I think that you have got the UNOS data and the patients that you follow for a year can be compared to them, and that is what you intended by saying you want to follow a cohort post-transplant for a year, is that not right?

DR. TRACY: Let me just read what is here on page 74 under No. 8, Proposed Post-Approval Follow-up.

SynCardia is proposing that follow-up be completed for all U.S. studies post-transplant patients out to one year and compare it to the UNOS registry data for survival. Additionally, clinical reliability will be evaluated on all implanted patients to further characterize any problems associated with the device.

The results of both the one-year survival and the customer complaints will be reported in the annual report to the PMA.

So, the proposal, as I am reading it here, I believe is saying follow the original cohort to one year.

DR. WEINBERGER: One year post-transplant.

DR. TRACY: One year post-transplant.

Is that enough or do we want the original cohort plus an additional group of patients for one year?

DR. WEINBERGER: I think we really need an additional cohort of patients.

DR. TRACY: I think it is reasonable. There are enough issues about this. We don't know

what sewing this thing to the atrial tissue does to the suture line at 9 months, so I think it is reasonable to ask that the patients who are implanted, I don't think this should go forever, but some reasonable amount of time, such as a year, all patients implanted within a year should be included and followed out to a year post-transplant.

Does that seem appropriate?

DR. HIRSHFELD: Yes, and I think it is important that we find out to what degree the real world can replicate what the investigator group has done. They are a very sophisticated group, they work very hard on taking care of these patients, and it would be nice to find out that all the other transplant programs in the country do as well.

DR. YANCY: Cindy, let me just raise two questions just for my own naive purposes, because I am still fairly new at this.

Even if we are able to effect a post-market surveillance or study or registry, what happens with those data, are they systematically reviewed by this body or another body, are we working in some futility or working towards some target?

The second question is as I look at what is stated, there is nothing that captures any of the pre-implant characteristics. Again, maybe that is too cumbersome. By the same token, this will be a relatively low volume procedure. Everything that is stated here starts with the time of implant and moves forward.

DR. TRACY: I will let the FDA answer the first part of the question, but I think obviously, part of the surveillance would include defining who is actually receiving the device, so the point of entry into the system would include indications for device implant, and then follow-up through that one-year period.

I will let Dr. Zuckerman answer the first part of the question.

DR. ZUCKERMAN: Right. Our Post-Market Branch would carefully review these data. In the event that we do see problems, potentially, it would help us rewrite the label, warnings, precautions, or if we think there are very significant problems, we could bring these data back to the advisory panel for your review. So, there is, in effect, a feedback mechanism.

DR. TRACY: That concludes the written

questions that the FDA had proposed to us, but, Dr. Zuckerman, is there any additional comments or questions before we move to the vote, that the FDA has?

DR. ZUCKERMAN: Not from the FDA.

DR. TRACY: I would like to ask the sponsor representatives if the company has any additional comments or questions before the vote?

DR. SLEPIAN: I would just like to say that there is a need for devices for end-stage heart failure patients that are at imminent risk of dying.

We have demonstrated with data the value of a technology like this for these kind of patients with adverse event rates that are comparable to other kinds of devices used for ill patients in Class IV heart failure.

I would just like to thank the FDA for their months of arduous review, we have worked closely with them, for their hours of labor that have been spent in analyzing our data, summarizing it, and re-presenting it.

I would also like to publicly thank the panel members assembled here for careful consideration and good discussion about a lot of

points that have come up regarding the use of this device.

Thank you very much.

DR. TRACY: Thank you.

I would like to ask our industry rep and our consumer rep if they have any comments or questions to make at this point before we move on.

Ms. Wells?

MS. WELLS: I have no additional.

DR. TRACY: Mr. Morton?

MR. MORTON: No, not from me.

Open Public Hearing

DR. TRACY: At this point, we will have our second open public hearing. I would like to ask the audience if there is anyone who wishes to address the panel on today's topic before we move on to the vote.

There are two people who have requested to make comments at this point.

I will invite Dr. Jarvik to come forward, please.

DR. JARVIK: Thank you. I know it is very late in the day. My name is Dr. Jarvik. I have nothing to do with the company, haven't had anything to do with this device for the last 17

years.

I want to raise a very serious prospect for the panel to consider, and that is the question of home use. There has been practically no discussion of that, but this device is extremely easy to control, it is definitely practical with the existing console as they have it, to outfit a home, so that it is safe to use.

It is not a given that having alarms in a hospital setting are necessarily going to be heard by the nurses. In our newer heart, had a cable cut by a portable x-ray machine in a hospital that ran over it, people make mistakes everywhere, and the home setting can possibly and reasonably be set up.

So, what I want to ask the panel is if they might make a statement of no objection, not in support of this, but of no objection if between the company and the FDA, they want to propose a program to certify home use, that that might be done.

I really think it is very, very important. I think the availability to patients is limited if they are essentially required to remain in the hospital. I think it is questionable legally whether you can approve a device that mandates that a patient who is healthy enough cannot return to

their home.

So, I would ask that the panel consider a very broad statement of no objection if the company and the FDA together want to add to this the ability to use it at home and remove the home use from the labeling.

Thank you.

DR. AZIZ: Can I make a comment?

DR. TRACY: I believe Dr. El-Banayosy has also asked for a few moments here.

DR. El-BANAYOSY: Comment at this point or our experience?

DR. TRACY: I am sorry?

DR. El-BANAYOSY: You asked me to comment at this point?

DR. TRACY: Yes, why don't you comment, make your comments that you had intended for the open public hearing.

DR. El-BANAYOSY: Thank you.

I want to comment at this point mentioned by Dr. Jarvik. I think I agree with him that we need a console to send the patient home, because the quality of life of this patient, at least in our experience, which is very good, the only limiting factor to send patients home is the big

console, and there is imminent need for small driver to send those patients home.

Back to our experience, as I mentioned before, I work in the heart center in Bad Oeyenhausen as the medical leader of the mechanical circulatory support teams. That is our team. That is also point mentioned before. That is a very important point to have a team taking care of those patients, and the team is having surgeons, coordinators, and clinical data manager, and so on.

We started with the program in September 1987, and we have near 800 patients supported with different devices. Why we have all the devices, because we have different kinds of patients, and we need those devices because the variety of patients we are dealing with them cannot be supported with one device, and that is why we have all these toys in our institution.

We are not playing with them. We are trying to select appropriate device for the particular patient to give him the best chance to survive.

As you see, we have 41 patients supported with the CardioWest, and we put the CardioWest patient in the worst cases in our institution. If

you allow me to show you this slide, look please to the risk factors we had in our patient cohort supported with the CardioWest.

You see 73 percent of our patients needed ventilation before we put the CardioWest on them, and we have more than half of the patients had previous acute renal failure before we put the CardioWest on them, and 40 percent of the patients had previous mechanical circulatory support system.

When I ask any panel of experts about the survival rate of those patients without putting the device in them, I think the answer will be definitely more than 90 percent death rate under such core of patients.

Well, that is the etiology that is similar to the etiology of the cardiogenic shock and the patient needed mechanical circulatory support.

We have significant number of patients for massive acute myocardial infarction, and those patients with acute myocardial infarction were in persistent cardiogenic shock, referred to our hospital from other cardiology department after being treated with multiple inotropes and intra-aortic balloon pump, even a significant number of them couldn't be transferred to our

institution without having support in their home hospital.

We went there and put those patients in femoral bypass because it was a hemodynamic instability, and we transferred them to our institutions. That reflects how sick those patients were before we put the system on them.

The last point, despite the fact that 40 percent of the patients had a mechanical circulatory support devices before we put the system in, that means we have partially removed most of the ventricle, and the median values was more than 400 picogram, which is quite high and up to 2,700.

What we saw in those patients after putting the devices in, we had a decrease in the level to 90 percent. That means we still have 10 percent from this value was detected on those patients. Why we had these values, that is a matter of further research.

I know that is not allowed to mention the results here, but we have a bleeding complication about 20 percent. We have a thromboembolic linearized rate of 0.04. In our institution, we have driveline infection, we have 3 cases, and 1

case of mediastinitis. That is regarding the infection complication.

That is one of the hearts we explanted and put the CardioWest in the patient. This patient had a volume reduction operation two years before we put the CardioWest on him, and interestingly, we had this kind of infection. It was not clinically detected in the patient before we put the system in, and that is a surprising and interesting finding which we had never seen before.

Regarding to the outcome, we have about 50 percent. This is a patient we supported with this system, and we have some of our patients, we have four of them right now at home, and we have some patients waiting for a heart in the hospital. They are waiting at home with the modified smaller console from X-Score Bell and Hart.

That is some of our patients supported with the system in our institutions, younger and old guys.

At this point, I wanted to add that we analyzed the patients supported with the CardioWest following acute cardiogenic shock followed by acute myocardial infarction and patients supported with other devices.

We have at our institution 36 patients supported following cardiogenic shock, and 26 patients were supported with other devices, and we have 10 patients supported with total artificial heart. We had a mortality rate and the patients supported with other mechanical device, 65 percent versus 20 percent. This is on a patient supported with a total artificial heart.

Thank you very much.

DR. TRACY: Thank you.

Is there anybody else in the audience that would like to make a comment at this time?

If not, we will close the open public hearing, and I would like to give the sponsor one last opportunity if they have any additional comments that they would like to make.

DR. SLEPIAN: Just to say thank you again, that's all.

DR. TRACY: Thank you.

We will move on to the vote and Geretta Wood will give us our options here.

Recommendation and Vote

MS. WOOD: Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990,

allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications or PMAs that are filed with the agency.

The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions of intended use outweigh any probable risks.

Effectiveness is defined as reasonable assurance that as in a significant portion of the population, the use of the device for its intended uses and conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows:

1. Approval if there are no conditions attached.

2. Approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions, such as physician

or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the panel.

3. Not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe, or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting, the Chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. TRACY: The panel will now prepare to vote. The recommendation of the panel may be, once again, approval, approval with conditions that are to be met by the applicant, or denial of approval.

I will now ask for a motion from the panel regarding the PMA.

Dr. Maisel.

DR. MAISEL: I would like to make a motion that we approve with conditions.

DR. TRACY: Second? Okay.

Now, at this point, we will state what the

conditions are, and just briefly, again to go through this, because it is a little confusing.

We will hear the conditions. They will be stated, then, we will discuss the conditions and vote individually on the conditions before we actually vote on the original motion.

Is there a condition to approval that somebody wants to bring up?

DR. WHITE: I think the first condition would be the post-market approval amendment that we discussed.

DR. TRACY: Post-market surveillance?

DR. WHITE: Yes.

DR. TRACY: So, the condition, if I can just state that, the first condition to approval would be that there would be post-market surveillance that would include all patients entering, from point of entry, for a year after the approval, and to follow those patients for a year, a year post-transplant, looking at adverse events either acutely related to the device or for that one year following transplantation.

Have I stated that correctly?

Any discussion on that?

DR. MAISEL: Do we want to say all